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APPLICANT: EVOLUTIONARY GENOMICS, LLC ET AL.

APPLN. NO.: PCT/US03/36247

FILED: NOVEMBER 3, 2003

FOR: DEVELOPMENT OF TERAPEUTICS FOR THE TREATMENT OF ENDOTOXIN-MEDIATED DISEASES

Mail Stop PCT
P.O. Box 1450
Alexandria, VA 22313-1450
Attention: IPEA/US

Dear Sir:

AMENDMENT UNDER ARTICLE 34

Please amend the application as follows:

Please replace pages 4, 10, 21 and 27 with the enclosed replacement pages. On page 4, line 12, the correct SEQ. ID. NOS. have been inserted. Also on page 4, Table 1 has been corrected whereby the species are correlated with the correct SEQ. ID. NOS. These changes are supported by the original Sequence Listing supplied with the application. On page 4, line 25, "Ka-Ks" is replaced with "Ka>Ks"; on line 27, "Ka-Ks" is replaced with "Ka<Ks"; these changes are obvious and consistent within the context of the sentences containing these corrections.

Replacement page 10, lines 13-20, contain obvious corrections to the descriptions of the figures. These changes are supported by the original Sequence Listing filed with the application and the original figures.

Replacement page 21, line 29, has a correction to the SEQ. ID NOS. which is supported by the original Sequence Listing provided with the application.

Replacement page 27, lines 22-34, has insertions of SEQ. ID NOS. in claims 12 and 13. Support for these insertions is provided by the original Sequence Listing provided with the application.

Replacement Figure 1 has SEQ. ID. NOS. inserted at the end of each polypeptide sequence. These corrections are supported by the original Sequence Listing filed with the application. Figure 1 also has an enlarged font.

Replacement Figures 2-9 have SEQ. ID. NOS. which are supported by the original Sequence Listing. They also have an enlarged font and the sequence has been divided into 10-nucleotide fragments.

It is believed that no fee is due with this submission. If this is in error, please charge any necessary fees to Deposit Account No. 19-5117.

Respectfully submitted,

Date: May 28, 2004

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result of subtle differences in the TLR4 protein. Thus, information about the specific amino acid replacements that occurred during evolution could provide unparalleled insights into the mechanism by which baboons and rhesus monkeys resist LPS-induced septic shock while maintaining functional innate immunity.

Published *TLR4* sequences from human (GenBank AF177765, XM_057452, U88880, and U93091), bonobo (GenBank AF179220), and baboon (GenBank AF180964) were used to design primers for polymerase chain reaction (PCR) amplification of a set of *TLR4* homologs from various primates. The primate *TLR4* homologs that were amplified and sequenced included rhesus monkey, gorilla, chimpanzee, gibbon, squirrel monkey, and capuchin. In addition, *TLR4* was amplified and sequenced from human, bonobo, and baboon and the published sequences for these species were confirmed (SEQ ID NOS: 1-24). As noted in Table 1, in most cases only exons 2 and 3 were sequenced (these include the full coding region of the *TLR4* gene).

Table 1 *TLR4* Sequences

SEQ ID NOS. 1-3	SEQ ID NOS. 4-6	SEQ ID NOS. 7-9	SEQ ID NOS. 10-12	SEQ ID NOS. 13-15	SEQ ID NOS. 16-18	SEQ ID NOS. 19-21	SEQ ID NOS. 22-24
Chimpanzee *Exons 2&3*	**Gorilla** *Exons 2&3*	**Gibbon** *Exons 2&3*	**Rhesus monkey** *Exons 2&3*	**Capuchin** *Exon 3*	**Squirrel monkey** *Exon 3*	**Baboon** *Exons 2&3*	**Bonobo** *Exons 2&3*

These sequences were aligned and a series of molecular evolution analyses were then performed. Included in these analyses were Ka/Ks pairwise comparisons for each of these genes. Such pairwise comparisons calculate the differences between values of nonsynonymous nucleotide substitutions per nonsynonymous site (Ka) to synonymous substitutions per synonymous site (Ks). Ka values statistically significantly greater than the corresponding Ks values (Ka>Ks) strongly suggest the action of positive selection. Conversely, Ka values statistically significantly less than the corresponding Ks values (Ka<Ks) strongly suggest the action of negative selection,

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an alignment of TLR4 protein sequences for the region of the protein that flanks the Asp299 residue from a number of mammalian species. Amino acid residues are shown in the single letter IUPAC code. Residues that are identical in all species examined are shown in bold. Dashes have been introduced (where insertions or deletions have occurred) to maximize the alignment. The critical residue (human Asp299, baboon Asn299) is shown in lower case. Note that this Asp residue is conserved in all mammal species examined, with the exception of the biochemically-conservative Asn replacement in the Old World monkeys baboon and rhesus (and, importantly, the non-functional human null mutant).

Figure 2 is the nucleotide sequence for baboon *TLR4* exons 2 and 3.
Figure 3 is the nucleotide sequence for bonobo *TLR4* exons 2 and 3.
Figure 4 is the nucleotide sequence for gibbon *TLR4* exons 2 and 3.
Figure 5 is the nucleotide sequence for gorilla *TLR4* exons 2 and 3.
Figure 6 is the nucleotide sequence for rhesus monkey *TLR4* exons 2 and 3.
Figure 7 is the nucleotide sequence for chimpanzee *TLR4* exons 2 and 3.
Figure 8 is the nucleotide sequence for capuchin *TLR4* exon 3.
Figure 9 is the nucleotide sequence for squirrel monkey *TLR4* exon 3.

DETAILED DESCRIPTION OF THE INVENTION

The subject invention relates to a method of identifying a nucleotide change in a TLR4 polynucleotide sequence of an Old World monkey wherein such change may be associated with reduced sensitivity to Gram-negative bacterial infection. This method involves the comparison of the TLR4 polynucleotide sequence from the Old World monkey with corresponding TLR4 polynucleotide sequence of a human to identify a polynucleotide change in said Old World monkey's TLR4 sequence that is evolutionarily meaningful. The evolutionarily meaningful change may then be associated with reduced sensitivity to Gram-negative bacterial infection. In particular, the evolutionarily meaningful change is from Asp299 in the human to Asn299 in the rhesus monkey or baboon.

The subject invention also includes a method of identifying a therapeutic agent that reduces sensitivity to Gram-negative bacterial infection. This method comprises

The amount of agent which will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, which can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness or advancement of the disease or condition, and should be decided according to the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems. For example, an effective amount of an agent identified according to the subject methods is readily determined by administering graded doses of the agent and observing the desired effect.

The following examples are provided to further assist those of ordinary skill in the art. Such examples are intended to be illustrative and therefore should not be regarded as limiting the invention. A number of exemplary modifications and variations are described in this application and others will become apparent to those of skill in this art. Such variations are considered to fall within the scope of the invention as described and claimed herein.

Example 1. PCR amplification and DNA sequencing of primate *TLR4* sequences.

Published *TLR4* sequences from human (GenBank AF177765, XM_057452, U88880, and U93091), bonobo (GenBank AF179220), and baboon (GenBank AF180964) were used to design primers (by methods well-known to those skilled in the art) for polymerase chain reaction (PCR) amplification of a set of *TLR4* homologs from various primates. The primate *TLR4* homologs that were PCR amplified and DNA sequenced (by methods well-known to those skilled in the art) included rhesus monkey, gorilla, chimpanzee, gibbon, squirrel monkey, and capuchin. In addition, *TLR4* was amplified and sequenced from human, bonobo, and baboon and the published sequences for these species were confirmed (SEQ ID NOS: 1 to 24). Because exons 2 and 3 contain the full coding region of the *TLR4* gene, in most cases only exons 2 and 3 were sequenced. These sequences were aligned by methods well-known to those skilled in the art.

8. The method of claim 6, wherein said substantial reduction in sensitivity to Gram-negative bacterial infection is determined by an indicator selected from the group consisting of:

(a) elimination or substantial reduction in host systemic inflammatory response to LPS in a human, non-human primate, or suitable animal model; and

(b) elimination or reduced severity of central nervous system dysfunction, adult respiratory distress syndrome, liver failure, acute renal failure, and/or disseminated intravascular coagulation in a human, non-human primate, or suitable animal model.

9. A method for treating sepsis, severe sepsis or septic shock in a primate, comprising:

administering to a primate in need thereof an effective dose of a therapeutic agent identified according to the method of claim 6.

10. A method for treating asthma in a primate, comprising:

administering to a primate in need thereof an effective dose of a therapeutic agent identified according to the method of claim 6.

11. A therapeutic agent identified according to the method of claim 6.

12. A composition comprising a polynucleotide selected from the group consisting of chimpanzee *TLR4* polynucleotide (SEQ. ID. NO. 1), gorilla *TLR4* polynucleotide (SEQ. ID. NO. 4), gibbon *TLR4* polynucleotide (SEQ. ID. NO. 7), rhesus monkey *TLR4* polynucleotide (SEQ. ID. NO. 10), capuchin *TLR4* polynucleotide (SEQ. ID. NO. 13), squirrel monkey *TLR4* polynucleotide (SEQ. ID NO. 16), and baboon *TLR4* polynucleotide (SEQ. ID NO. 19).

13. A composition comprising a polypeptide selected from the group consisting of chimpanzee TLR4 polypeptide (SEQ. ID. NO. 3), gorilla TLR4 polypeptide (SEQ. ID. NO. 8), gibbon TLR4 polypeptide (SEQ. ID. NO. 9), rhesus monkey TLR4 polypeptide (SEQ. ID. NO. 12), capuchin TLR4 polypeptide (SEQ. ID. NO. 15), squirrel monkey TLR4 polypeptide (SEQ. ID NO. 18), and baboon TLR 4 polypeptide (SEQ. ID NO. 21).

Species		SEQ ID NO
Human	CNLT**I**EE**FR**LTYLD-YYLDdIIDLFNC**LA**NAS**S**FS**L**-	25
Human null	CNLT**I**EE**FR**LTYLD-YYLDgIIDLFNC**LA**NAS**S**FS**L**-	26
Chimpanzee	CNLT**I**EE**FR**LTYLD-YYLDdIIDLFNC**LA**NAS**S**FS**L**-	27
Bonobo	CNLT**I**EE**FR**LTYLD-YYLDdIIDLFNC**LA**NAS**S**FS**L**-	28
Gorilla	CNLT**I**EE**FR**LTYLD-YYLDdIIDLFNC**LA**NAS**S**FS**L**-	29
Orangutan	CNLT**I**EE**FR**LAYLD-YYLDdIIDLFNC**LA**NVS**S**FS**L**-	30
Gibbon	CNLT**I**EE**FR**LTYLD-YYLDdIIDLFNC**LA**NAS**S**FS**L**-	31
Baboon	CNLT**I**EE**FR**LTYLD-YYLDnIIDLFNC**LA**NAS**S**FS**L**-	32
Rhesus	CNLT**I**EE**FR**LTYLD-YYLDnIIDLFNC**LA**NAS**S**FS**L**-	33
Horse	HNLT**I**EE**FR**LAYIDNYSSKdSIDLLNC**LA**DI**S**KI**SL**-	34
Cow	CNLT**I**EQ**FR**IAYLDKFSGDd-TDLFNC**LA**NV**S**VI**SL**-	35
Cat	CNLI**I**EK**FR**IAYFDKFS-EdAIDSFNC**LA**NV**S**TI**SL**-	36
Dog	CNLT**I**EK**FR**IAYFDSFS-KdTTNLFNQ**L**VNI**S**AI**SL**-	37
Hamster	CKVT**I**EE**FR**FTYANEFS-EdITD-FDC**LA**NV**S**AM**SL**-	38
Rat	CNVS**I**DE**FR**LTYINHFS-DdIYN-LNC**LA**NI**S**AM**S**F-	39
Mouse	CDVT**I**DE**FR**LTHTNDFS-DdI-VKFHC**LA**NV**S**AM**SL**-	40

Figure 1.

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Baboon CDS

GTGGTTCCTAACATTACTTATCAATGCATGGAGCTGAATTTCTACAAAATC
CCCGACAACATCCCCTTCTCAACCAAGAACCTGGACCTGAGCTTTAATCC
CCTGAGGCATTTAGGCAGCTATAGCTTCCTCCGTTTTCCAGAACTGCAGGT
GCTGGATTTATCCAGGTGTGAAATCCAGACAATTGAAGATGGGGCATATC
AGAGCCTAAGCCACCTCTCCACCTTAATATTGACAGGAAACCCCATCCAG
AGTTTAGCCCTGGGAGCCTTTTCTGGACTATCAAGTTTACAGAAGCTGGTG
GCTGTGGAGACAAATCTAGCATCTCTAGAGAACTTCCCCATTGGACATCT
CAAAACTTTGAAAGAACTTAATGTGGCTCACAATCTTATCCAGTCTTTCAA
ATTACCTGAGTATTTTTCTAATCTGACCAATCTAGAGCACTTGGACCTTTC
CAGTAACAAGATTCAAAATATTTATTGCAAAGACTTGCAGGTTCTACATC
AAATGCCCCTACCCAATCTCTCTTTAGACCTGTCCCTGAACCCTATAAACT
TTATCCAACCAGGTGCATTTAAAGAAATTAGGCTTCATAAGCTGACTTTGA
GAAGTAATTTTGATGATTTAAATGTAATGAAAACTTGTATTCAAGGTCTGG
CTGGTTTAGAAGTCCATCGTTTGGTTCTGGGAGAATTTAGAAATGAAAGA
AACTTGGAAGAGTTTGACAAATCTGCTCTGGAGGGATTGTGCAATTTGAC
CATTGAAGAATTCCGATTAACATACTTAGACTACTACCTCGATAATATTAT
TGACTTATTTAATTGTTTGGCAAATGCTTCTTCATTTTCCCTGGTGAGTGTG
AATATTAAAAGGGTAGAAGACTTTTCTTATAATTTCAGATGGCAACATTTA
GAATTAGTTAACTGTAAATTTGAACAGTTTCCCACATTGGAACTCGAATCT
CTCAAAAGGCTTACTTTCACTGCCAACAAAGGTGGGAATGCCTTTTCAGA
AGTTGATCTACCAAGCCTTGAGTTTCTAGATCTCAGTAGAAATGGCTTGAG
TTTCAAAGGTTGCTGTTCTCAAAGTGATTTTGGGACAACCAGCCTAAAGTA
TTTAGATCTGAGCTTCAATGATGTTATTACCATGGGTTCAAACTTCTTGGG
CTTAGAACAACTAGAACATCTGGATTTCCAGCATTCCAATTTGAAACAGA
TGAGTCAATTTTCAGTATTCCTATCACTCAGAAACCTCATTTACCTTGACA
TTTCTCATACTCACACCACAGTTGCTTTCAATGGCATTTTCGATGGCTTGCT
CAGTCTCAAAGTCTTAAAAATGGCTGGCAATTCTTTCCAGGAAAACTTCCT
TCCAGATATCTTCACAGATCTGAAAAACTTGACCTTCCTGGACCTCTCTCA
GTGTCAACTGGAGCAGTTGTCTCCAACAGCATTTGACACACTCAACAAGC
TTCAGGTACTAAATATGAGCCACAACAACTTCTTTTCATTGGATGTGTTTC
CTTATAAGTGTCTGCCCTCCCTCCAGGTTCTCGATTACAGTCTCAATCACA
TAATGACTTCCAAAAACCAGGAACCTCAGCATTTTCCAAGTAGTCTAGCTT
TCTTAAATCTTACTCAGAATGACTTTGCTTGTACTTGTGAACACCAGAGTT
TCCTGCAGTGGATCAAGGACCAGAGGCAGCTCTTGGTGGAAGCTGAACGA
ATGGAATGTGCAACACCTTCAGATAAACAGGGCATGCCTGTGCTGAGTGT
GAATATTACCTGTCAGATGAATAAGACCATCATTGGTGTGTCTGTGTTCAG
TGTGCTTGTGGTATCTGTTGTAGCAGTTCTGGTCTATAAGTTCTATTTTCAC
CTGATGCTTCTTGCTGGCTGCATAAAGTATGGTAGAGGTGAAAACATCTA
TGATGCCTTTGTTATCTACTCAAGCCAGGATGAGGACTGGGTAAGGAATG
AGCTAGTAAAGAATTTAGAAGAAGGGGTGCCTCCCTTTCAGCTCTGCCTT
CACTACAGAGACTTTATTCCCGGTGTGGCCATTGCTGCAAACATCATCCAT
GAAGGTTTCCATAAAAGCCGAAAGGTGATTGTTGTGGTGTCCCAGCACTT
CATCCAGAGCCGCTGGTGTATCTTTGAATATGAGATTGCTCAGACCTGGC
AGTTTCTGAGCAGTCGTGCAGGCATAATCTTCATTGTCCTGCAGAAGGTG
GAGAAGACCCTGCTCAGGCAGCAGGTGGAGCTGTACCGCCTTCTCAGCAG

GAACACTTACCTGGAGTGGGAGGACAGTGTCCTAGGGCAGCACATCTTCT
GGAGACGACTCAGAAAAGCCCTGTTGGATGGCAGATCGTGGAATCCAGA
AGAACAGTAG

FIGURE 2
(SEQ ID NO. 19)

Bonobo

GTGGTTCCTAATATTACTTATCAATGCATGGAGCTGAATTTCTACAAAATCCCCGACAACC
TCCCCTTCTCAACCAAGAACCTGGACCTGAGCTTTAATCCCCTGAGGCATTTAGGCAGCTA
TAGCTTCTTCAGTTTCCCAGAACTGCAGGTGCTGGATTTATCCAGGTGTGAAATCCAGACA
ATTGAAGATGGGGCATATCAGAGCCTAAGCCACCTCTCCACCTTAATATTGACAGGAAAC
CCCATCCAGAGTTTAGCCCTGGGAGCCTTTTCTGGACTATCAAGTTTACAGAAGCTGGTGG
CTGTGGAGACAAATCTAGCATCTCTAGAGAACTTCCCCATTGGACATCTCAAAACTTTGAA
AGAACTTAATGTGGCTCACAATCTTATCCAATCTTTCAAATTACCTGAGTATTTTTCTAATC
TGACCAATCTAGAGCACTTGGACCTTTCCAGCAACAAGATTCAAAGTATTTATTGCACAG
ACTTGCGGGTTCTACATCAAATGCCCCTACTCAATCTCTCTTTAGACCTGTCCCTGAACCCT
ATGAACTTTATCCAACCAGGTGCATTTAAAGAAATTAGGCTTCATAAGCTGACTTTGAGA
AATAATTTTGATAGTTTAAATGTAATGAAAACTTGTATTCAAGGTCTGGCTGGTTTAGAAG
TCCATCGTTTGGTTCTGGGAGAATTTAGAAATGAAGAAAACTTGGAAAAGTTTGACAAAT
CTGCTCTAGAGGGCCTGTGCAATTTGACCATTGAAGAATTCCGATTAGCATACTTAGACTA
CTACCTCGATGATATTATTGACTTATTTAATTGTTTGACAAATGTTTCTTCATTTTCCCTGG
TGAGTGTGACTATTAAAAGCGTAAAAGACTTTTCTTATAATTTCGGATGGCAACATTTAGA
ATTAGTTAAGTGTAAATTTGGACAGTTTCCCACATTGAAACTCAAATCTCTCAAAAGGCTT
ACTTTCACTTCCAACAAAGGTGGGAATGCTTTTTCAGAAGTTGATCTACCAAGCCTTGAGT
TTCTAGATCTCAGTAGAAATGGCTTGAGTTTCAAAGGTTGCTGTTCTCAAAGTGATTTTGG
GACAACCAGCCTAAAGTATTTAGATCTGAGCTTCAATGGTGTTATTACCATGAGTTCAAAC
TTCTTGGGCTTAGAACAACTAGAACATCTGGATTTCCAGCATTCCAATTTGAAACAAATGA
GTGAGTTTTCAGTATTCCTATCACTCAGAAACCTCATTTACCTTGACATTTCTCATACTCAC
ACCAGAGTTGCTTTCAATGGCATCTTCAATGGCTTGTCCAGTCTCGAAGTCTTGAAAATGG
CTGGCAATTCTTTCCAGGAAAACTTCCTTCCAGATATCTTCACAGAGCTGAGAAACTTGAC
CTTCCTGGACCTCTCTCAGTGTCAACTGGAGCAGTTGTCTCCAACAGCATTTAACTCACTC
TCCAGTCTTCAGGTACTAAATATGAGCCACAACAACTTCTTTTCATTGGATACGTTTCCTT
ATAAGTGTCTGAACTCCCTCCAGGTTCTTGATTACAGTCTCAATCACATAATGACTTCCAA
AAAACAGGAACTACAGCATTTTCCAAGTAGTCTAGCTTTCTTAAATCTTACTCAGAATGAC
TTTGCTTGTACTTGTGAACACCAAAGTTTCCTGCAATGGATCAAGGACCAGAGGCAGCTCT
TGGTGGAAGTTGAACGAATGGAATGTGCAACACCTTCAGATAAGCAGGGCATGCCTGTGC
TGAGTTTGAATATCACCTGTCAGATGAATAAGACCATCATTGGTGTGTCGGTCCTCAGTGT
GCTTGTAGTATCTGTTGTAGCAGTTCTGGTCTATAAGTTCTATTTTCACCTGATGCTTCTTG
CTGGCTGCATAAAGTATGGTAGAGGTGAAAACATCTATGATGCCTTTGTTATCTACTCAAG
CCAGGATGAGGACTGGGTAAGGAATGAGCTAGTAAAGAATTTAGAAGAAGGGGTGCCTC
CATTTCAGCTCTGCCTTCACTACAGAGACTTTATTCCCGGTGTGGCCATTGCTGCCAACAT
CATCCATGAAGGTTTCCATAAAAGCCGAAAGGTGATTGTTGTGGTGTCCCAGCACTTCATC
CAGAGCCGCTGGTGTATCTTTGAATATGAGATTGCTCAGACGTGGCAGTTTCTGAGCAGTC
GTGCTGGTATCATCTTCATTGTCCTGCAGAAGGTGGAGAAGACCCTGCTCAGGCGGCAGG
TGGAGCTGTACCGCCTTCTYAGCAGGAACACTTACCTGGAGTGGGAGGACAGTGTCCTGG
GGCGGCACATCTTCTGGAGACGACTCAGAAAAGCCCTGCTGGATGGTAAATCATGGAATC
CAGAAGGAACAGTGGGTACAGGATGCAATTGGCAGGAAGCAACATCTATCTGA

FIGURE 3

Gibbon

GTGGTTCCTAACATTACTTATCAATGCATGGAGCTGAATTTCTACAAAATCCCCGACAACC
TCCCCTTCTCAACCAAGAACCTGGACCTGAGCTTTAATCCCCTGAGGCATTTAGGCAGCTA
TAGCTTCTTCAGTTTCCCAGAACTGCAGGTGCTGGATTTATCCAGGTGTGAAATCCAGACA
ATTGAAGATGGGGCATATCAGAGCCTAAGCCTCCTCTCCACCTTAATATTGACAGGAAAC
CCCATCCAGAGTTTAGCTCTGGGAGCCTTTTCTGGACTATCAAGTTTACAGAAGCTAGTGG
CTGTGGAGACAAATCTAGCATCTCTAGAGAACTTCCCCATTGGACATCTCAAAACTTTGAA
AGAACTTAATGTGGCTCACAATCTTATCCAATCTTTCAAATTACCTGAGTATTTTTCTAATC
TGACCAATCTAGAGCACTTGGACCTTTCCAGCAACAAGATTCAAAGTATTTATTGCAAAG
ACTTGCAGGTTCTACATCAAATGCCCCTACTCAATCTCTCTTTAGACCTGTCCCTGAACCCT
ATGAACTTTATCCAACCAGGTGCATTTAAAGAAATTAGCCTTCRTAAGCTGACTTTAAGAA
ATAATTTTGATAGTTTAAATGTAATGAAAACTTGTATTCAAGGTCTGGCTGGTTTAGAAGT
CCATCGTTTGGTTCTGGGAGAATTTAGAAATGAAGGAAACTTGGAAGAGTTTGACAAATC
TGCTCTAGAGGGCCTGTGCAATTTGACCATTGAAGAATTCCGATTAGCATACTTAGACCAC
TACCTCGATGATATTATTGACTTATTTAATTGTTTGGCAAATGTTTCTTCATTTTCCCTGGT
GAGTGTGACTATTAAAAGGGTAGAAGACTTTTCTTATAATTTCGGATGGCAACATTTAGA
ATTAGTTAACTGTAAATTTGGACAGTTTCCCACATTGAACCTCAAATCTCTCAAAAGGCTT
ACTTTCACTGCCAACAGAGGTGGGAATGCTTTTTCAGAAGTTGATCTACCAAGCCTTGAGT
TTCTAGATCTCAGTAGAAATGGCTTGAGTTTCAAAGGTTGCTGTTCTCAAAGTGATTTTGG
GACAAACAGCCTAAAGTATTTAGATCTGAGCTTCAATGATGTTATTACCATGAGTTCAAAC
TTCTTGGGCTTAGAACAGCTAGAACATCTGGATTTGCAGCATTCCAATTTGAAACAAATGA
GTGAATTTTCAGTATTCCTATCACTCAGAAACCTCATTTACCTTGACATTTCTCATACTCAC
ACCAGAGTTGCTTTCAATGGCATCTTCAATGGCTTGTCCAATCTCGAAGTCTTGAAAATGG
CTGGCAATTCTTTCCAGGAAAACTTCCTTCCAGATATCTTCACAGAGCTGAGAAACTTGAC
CTTCCTGGACCTCTCTCAGTGTCAACTGGAGCAATTGTCTCCAACAGCATTTAACTCACTC
TCCAGTCTTCAGGTACTAAATATGAGCCACAACAACTTCTTTTCATTGGATACGTTTCCTT
ATAAGTGTCTGAACTCCCTCCAGGTTCTTGATTACAGTCTCAATCACATAATGACTTCCAA
AAAACAGGAACTACAGCGTTTTCCAAGTAGTCTAGCCTTCTTAAATCTTACTCAGAATGAC
TTTGCTTGTACTTGTGAACACGAGAGTTTCCTGCAGTGGATCAAGGACCAGAGGCAGCTCT
TGGTGGAAGTTGAACGAATGGAATGTGCAACACCTTCAGATAAGCAGGGCATGCCTGTGC
TGAGTTTGAATATCACCTGTCAGATGAATAAGACCATCATTGGTGTGTCAGTCCTCAGTGT
GCTTGTAGTATCTGTTGTAGCAGTTCTGGTCTATAAGTTCTATTTTCACCTGATGCTTCTTG
CTGGCTGCATGAAGTATGGTAGAGGTGAAAACACCTATGATGCCTTTGTTATCTACTCCAG
CCAGGATGAGGACTGGGTAAGGAATGAGCTAGTAAAGAATTTAGAAGAAGGGGTGCCTC
CCTTTCAGCTCTGCCTTCACTACAGAGACTTTATTCCYGGTGTGGCCATTGCTGCCAACAT
CATCCATGAAGGTTTCCATAAAAGCCGAAAGGTGATTGTTGTGGTGTCCCAGCACTTCATC
CAGAGCCGCTGGTGTATCTTTGAGTATGAGATTGCTCAGACCTGGCAGTTTCTGAGCAGTC
ATGCTGGGATCATCTTCATTGTCCTGCAGAAGGTGGAGAAGACCCTGCTCAGGCAGCAGG
TGGAGCTGTACCGCCTTCTCAGCAGGAACACTTACCTGGAGTGGGAGGATAGTGTCCTGG
GGCGGCACATTTTCTGGAGACGACTCAGAAAAGCCCTGCTGGATGGTAAATCATGGAATC
CAGAAGGAACAGTGGGTACAGGATGCAATTAG

FIGURE 4

Gorilla

GTGGTTCCTAATATTACTTATCAATGCATGGAGCTGAATTTCTACAAAATCCCCGACAACC
TCCCCTTCTCAACCAAGAACCTGGACCTGAGCTTTAATCCCCTGAGGCATTTAGGCAGCTA
TAGCTTCTTCAGTTTCCCAGAACTGCAGGTGCTGGATTTATCCAGGTGTGAAATCCAGACA
ATTGAAGATGGGGCATATCAGAGCCTAAGCCACCTCTCCACCTTAATATTGACAGGAAAC
CCCATCCAGAGTTTAGCCCTGGGAGCCTTTTCTGGACTATCAAGTTTACAGAAGCTGGTGG
CTGTGGAGACAAATCTAGCATCTCTAGAGAACTTCCCCATTGGACATCTCAAAACTTTGAA
AGAACTTAATGTGGCTCACAATCTTATTCAATCTTTCAAATTACCTGAGTATTTTTCTAATC
TGACCAATCTAGAGTACTTGGACCTTTCCAGCAACAAGATTCAAAGTATTTATTGCACAGA
CTTGCGGGTTCTACATCAAATGCCCCTACTCAATCTCTCTTTAGACCTGTCCCTGAACCCTA
TGACCTTTATCCAACCAGGTGCATTTAAAGAAATTAGGCTTCATAAGCTGACTTTGAGAAA
TAATTTTGATAGTTTAAATGTAATGAAAACTTGTATTCAAGGTCTGGCTGGTTTAGAAGTC
CGTCGTTTGGTTCTGGGAGAATTTAGAAATGAAGGAAACTTGGAAAAGTTTGACAAATCT
GCTCTAGAGGGCCTGTGCAATTTGACCATTGAAGAATTCCGATTAGCATACTTAGACTACT
ACCTCGATGATATTATTGACTTATTTAATTGTTTGACAAATGTTTCTTCATTTTCCCTGGTG
AGTGTGACTATTGAAAGGGTAAAAGACTTTTCTTATAATTTCGGATGGCAACATTTAGAAT
TAGTTAACTGTAAATTTGGACAGTTTCCCACATTGAAACTCAAATCTCTCAAAAGGCTTAC
TTTCACTTCCAACAAAGGTGGGAATGCTTTTTCGGAAGTTGATCTACCAAGCCTTGAGTTT
CTAGATCTCAGTAGAAATGGCTTGAGTTTCAAAGGTTGCTGTTCTCAAAGTGATTTTGGGA
CAACCAGCCTAAAGTATTTAGATCTGAGCTTCAATGGTGTTATTACCATGAGTTCAAACTT
CTTGGGCTTAGAACAACTAGAACATCTGGATTTCCAGCATTCCAATTTGAAACAAATGAG
TGAGTTTTCAGTATTCCTATCACTCAGAAACCTCATTTACCTTGACATTTCTCATACTCACA
CCAGAGTTGCTTTCAATGGCATCTTCAATGGCTTGTCCAGTCTCGAAGTCTTGAAAATGGC
TGGCAATTCTTTCCAGGAAAACTTCCTTCCAGATATCTTCACAGAGCTGAGAAACTTGACC
TTCCTGGACCTCTCTCAGTGTCAACTGGAGCAGTTGTCTCCAACAGCATTTAACTCACTCT
CCAGTCTTCAGGTACTAAATATGAGCCACAACAACTTCTTTTCATTGGATACGTTTCCTTA
TAAGTGTCTGAACTCCCTCCGGGTTCTTGATTACAGTCTCAATCACATAATGACTTCCAAA
AAACAGGAACTACAGCATTTTCCAAGCAGTCTAGCTTTCTTAAATCTTACTCAGAATGACT
TTGCTTGTACTTGTGAACACCAGAGTTTCCTGCAATGGATCAAGGACCAGAGGCAGCTCTT
GGTGGAAGTTGAACGAATGGAATGTGCAACACCTTCAGATAAGCAGGGCATGCCTGTGCT
GAGTTTGAATATCACCTGTCAGATGAATAAGACCATCATTGGTGTGTCGGTCCTCAGTGTG
CTTGTAGTATCTGTTGTAGCAGTTCTGGTCTATAAGTTCTATTTTCACCTGATGCTTCTTGC
TGGCTGCATAAAGTATGGTAGAGGTGAAAACGTCTATGATGCCTTTGTTATCTACTCAAGC
CAGGATGAGGACTGGGTAAGGAATGAGCTAGTAAAGAATTTAGAAGAAGGGGTGCCTCC
ATTTCAGCTCTGCCTTCACTACAGAGACTTTATTCCCGGTGTGGCCATTGCTGCCAACATC
ATCCATGAAGGTTTCCATAAAAGTCGAAAGGTGATTGTTGTGGTGTCCCAGCACTTCATCC
AGAGCCGCTGGTGTATCTTTGAATATGAGATTGCTCAGACCTGGCAGTTTCTGAGCAGTCG
TGCTGGTATCATCTTCATTGTCCTGCAGAAGGTGGAGAAGACCCTGCTCAGGCAGCAGGT
GGAGCTGTACCGCCTTCTCAGCAGGAACACTTACCTGGAGTGGGAGGACAGTGTCCTGGG
GCGGCACATCTTCTGGAGACGACTCAGAAAAGCCCTGCTGGATGGTAAATCATGGAATCC
AGAAGGAACAGTGGGTACAGGATGCAATTGGCAGGAAGCAACATCTATCTGA

FIGURE 5

10/532153

Rhesus monkey

GTGGTTCCTAATATTACTTATCAATGCATGGAGCTGAATTTCTACAAAATCCCCGACAACC
TCCCCTTCTCAACCAAGAACCTGGACCTGAGCTTTAATCCCCTGAGGCATTTAGGCAGCTA
TAGCTTCTTCAGTTTCCCAGAACTGCAGGTGCTGGATTTATCCAGGTGTGAAATCCAGACA
ATTGAAGATGGGGCATATCAGAGCCTAAGCCACCTCTCCACTTTAATATTGACAGGAAAC
CCCATCCAGAGTTTAGCCCTGGGAGCCTTTTCTGGACTATCAAGTTTACAGAAGCTGGTGG
CTGTGGAGACAAATCTAGCATCTCTAGAGAACTTCCCCATTGGACATCTCAAAACTTTGAA
AGAACTTAATGTGGCTCACAATCTTATCCAGTCTTTCAAATTACCTGAGTATTTTTCTAATC
TGACCAATCTAGAGCACTTGGACCTTTCCAGTAACAAGATTCAAAATATTTATTGCAAAG
ACTTGCAGGTTCTACATCAAATGCCCCTATCCAATCTCTCTTTAGACCTGTCCCTGAACCCT
ATAAACTTTATCCAACCAGGTGCATTTAAAGAAATTAGGCTTCATAAGCTGACTTTGAGA
AGTAATTTTGATGATTTAAATGTAATGAAAACTTGTATTCAAGGTCTGGCTGGTTTAGAAG
TCCATCGTTTGGTTCTGGGAGAATTTAGAAATGAAAGAAACTTGGAAGAGTTTGACAAAT
CTTCTCTGGAGGGATTGTGCAATTTGACCATTGAAGAATTCCGATTAACATACTTAGACTA
CTACCTCGATAATATTATTGACTTATTTAATTGTTTGGCAAATGTTTCTTCATTTTCCCTGG
TGAGTGTGAGTATTAAAAGGGTAGAAGACTTTTCTTATAATTTCAGATGGCAACATTTAGA
ATTAGTTAACTGTAAATTTGAACAGTTTCCCACATTGGAACTCGAATCTCTCAAAAGGCTT
ACTTTCACTGCCAACAAAGGTGGGAATGCTTTTTCAGAAGTTGATCTACCAAGCCTTGAGT
TTCTAGATCTCAGTAGAAATGGCTTGAGTTTCAAAGGTTGCTGTTCTCAAAGTGATTTTGG
GACAACCAGCCTAAAGTATTTAGATCTGAGCTTCAATGATGTTATTACCATGAGTTCAAAC
TTCTTGGGCTTAGAAAAACTAGAACATCTGGATTTCCAGCATTCCAATTTGAAACAGATGA
GTCAATTTTCAGTATTCCTATCACTCAGAAACCTCATTTACCTTGACATTTCTCATACTCAC
ACCAGAGTTGCTTTCAATGGCATCTTCGATGGCTTGCTCAGTCTCAAAGTCTTAAAAATGG
CTGGCAATTCTTTCCAGGAAAACTTCCTTCCAGATATCTTCACAGATCTGAAAAACTTGAC
CTTCCTGGACCTCTCTCAGTGTCAATTGGAGCAGTTGTCTCCAACAGCATTTGACACACTC
AACAAGCTTCAGGTACTAAATATGAGCCACAACAACTTCTTTTCATTGGATACGTTTCCTT
ATAAGTGTCTGCCCTCCCTCCAGGTTCTCGATTACAGTCTCAATCACATAATGACTTCCAA
CAACCAGGAACTACAGCATTTTCCAAGTAGTCTAGCTTTCTTAAATCTTACTCAGAATGAC
TTTGCTTGTACTTGTGAACACCAGAGTTTCCTGCAGTGGATCAAGGACCAGAGGCAGCTCT
TGGTGGAAGCTGAACGAATGGAATGTGCAACACCTTCAGATAAACAGGGCATGCCGGTGC
TGAGTTTGAATATTACCTGTCAGATGAATAAGACCATCATTGGTGTGTCTGTGTTCAGTGT
GCTTGTGGTATCTGTTGTAGCAGTTCTGGTCTATAAGTTCTATTTTCACCTGATGCTTCTTG
CTGGCTGCATAAASTATGGTAGAGGTGAAAACATCTATGATGCCTTTGTTATCTACTCAAG
CCAGGATGAGGACTGGGTAAGGAATGAACTAGTAAAGAATTTAGAAGAAGGGGTGCCTC
CCTTTCAGCTCTGCCTTCACTACAGAGACTTTATTCCCGGTGTGGCCATTGCTGCAAACAT
CATCCATGAAGGTTTCCATAAAAGCCGAAAGGTGATTGTTGTGGTGTCCCAGCACTTCATC
CAGAGCCGCTGGTGTATCTTTGAATATGAGATTGCTCAGACCTGGCAGTTTCTGAGCAGTC
GTGCAGGCATAATCTTCATTGTCCTGCAGAAGGTGGAGAAGACCCTGCTCAGGCAGCAGG
TGGAGCTGTACCGCCTTCTCAGCAGGAACACTTACCTGGAGTGGGAGGACAGTGTCCTGG
GGCAGCACATCTTCTGGAGACGACTCAGAAAAGCCCTGTTGGATGGCAGATCGTGGAATC
CAGAAGAACAGTAG

FIGURE 6

Chimpanzee

GTGGTTCCTAATATTACTTATCAATGCATGGAGCTGAATTTCTACAAAATCCCCGACAACC
TCCCCTTCTCAACCAAGAACCTGGACCTGAGCTTTAATCCCCTGAGGCATTTAGGCAGCTA
TAGCTTCTTCAGTTTCCCAGAACTGCAGGTGCTGGATTTATCCAGGTGTGAAATCCAGACA
ATTGAAGATGGGGCATATCAGAGCCTAAGCCACCTCTCCACCTTAATATTGACAGGAAAC
CCCATCCAGAGTTTAGCCCTGGGAGCCTTTTCTGGACTATCAAGTTTACAGAAGCTGGTGG
CTGTGGAGACAAATCTAGCATCTCTAGAGAACTTCCCCATTGGACATCTCAAAACTTTGAA
AGAACTTAATGTGGCTCACAATCTTATCCAATCTTTCAAATTACCTGAGTATTTTTCTAATC
TGACCAATCTAGAGCACTTGGACCTTTCCAGCAACAAGATTCAAAGTATTTATTGCACAG
ACTTGCGGGTTCTACATCAAATGCCCCTACTCAATCTCTCTTTAGACCTGTCCCTGAACCCT
ATGAACTTTATCCAACCAGGTGCATTTAAAGAAATTAGGCTTCATAAGCTGACTTTGAGA
AATAATTTTGATAGTTTAAATGTAATGAAAACTTGTATTCAAGGTCTGGCTGGTTTAGAAG
TCCATCGTTTGGTTCTGGGAGAATTTAGAAATGAAGGAAACTTGGAAAAGTTTGACAAAT
CTGCTCTAGAGGGCCTGTGCAATTTGACCATTGAAGAATTCCGATTAGCATACTTAGACTA
CTACCTCGATGATATTATTGACTTATTTAATTGTTTGACAAATGTTTCTTCATTTTCCCTGG
TGAGTGTGACTATTAAAAGCGTAAAAGACTTTTCTTATAATTTCGGATGGCAACATTTAGA
ATTAGTTAACTGTAAATTTGGACAGTTTCCCACATTGAAACTCAAATCTCTCAAAAGGCTT
ACTTTCACTTCCAACAAAGGTGGGAATGCTTTTTCAGAAGTTGATCTACCAAGCCTTGAGT
TTCTAGATCTCAGTAGAAATGGCTTGAGTTTCAAAGGTTGCTGTTCTCAAAGTGATTTTGG
GACAACCAGCCTAAAGTATTTAGATCTGAGCTTCAATGGTGTTATTACCATGAGTTCAAAC
TTCTTGGGCTTAGAACAACTAGAACATCTGGATTTCCAGCATTCCAATTTGAAACAAATGA
GTGAGTTTTCAGTATTCCTATCACTCAGAAACCTCATTTACCTTGACATTTCTCATACTCAC
ACCAGAGTTGCTTTCAATGGCATCTTCAATGGCTTGTCCAGTCTCGAAGTCTTGAAAATGG
CTGGCAATTCTTTCCAGGAAAACTTCCTTCCAGATATCTTCACAGAGCTGAGAAACTTGAC
CTTCCTGGACCTCTCTCAGTGTCAACTGGAGCAGTTGTCTCCAACAGCATTTAACTCACTC
TCCAGTCTTCAGGTACTAAATATGAGCCACAACAACTTCTTTTCATTGGATACGTTTCCTT
ATAAGTGTCTGAACTCCCTCCAGGTTCTTGATTACAGTCTCAATCACATAATGACTTCCAA
AAAACAGGAACTACAGCATTTTCCAAGTAGTCTAGCTTTCTTAAATCTTACTCAGAATGAC
TTTGCTTGTACTTGTGAACACCAAAGTTTCCTGCAATGGATCAAGGACCAGAGGCAGCTCT
TGGTGGAAGTTGAACGAATGGAATGTGCAACACCTTCAGATAAGCAGGGCATGCCTGTGC
TGAGTTTGAATATCACCTGTCAGATGAATAAGACCATCATTGGTGTGTCGGTCCTCAGTGT
GCTTGTAGTATCTGTTGTAGCAGTTCTGGTCTATAAGTTCTATTTTCACCTGATGCTTCTTG
CTGGCTGCATAAAGTATGGTAGAGGTGAAAACATCTATGATGCCTTTGTTATCTACTCAAG
CCAGGATGAGGACTGGGTAAGGAATGAGCTAGTAAAGAATTTAGAAGAAGGGGTGCCTC
CATTTCAGCTCTGCCTTCACTACAGAGACTTTATTCCCGGTGTGGCCATTGCTGCCAACAT
CATCCATGAAGGTTTCCATAAAAGCCGAAAGGTGATTGTTGTGGTGTCCCAGCACTTCATC
CAGAGCCGCTGGTGTATCTTTGAATATGAGATTGCTCAGACCTGGCAGTTTCTGAGCAGTC
GTGCTGGTATCATCTTCATTGTCCTGCAGAAGGTGGAGAAGACCCTGCTCAGGCGGCAGG
TGGAGCTGTACCGCCTTCTCAGCAGGAACACTTACCTGGAGTGGGAGGACAGTGTCCTGG
GGCGGCACATCTTCTGGAGACGACTCAGAAAAGCCCTGCTGGATGGTAAATCATGGAATC
CAGAAGGAACAGTGGGTACAGGATGCAATTGGCAGGAAGCAACATCTATCTGA

FIGURE 7

Capuchin

TGTGAAATCCACACAATTGAAGATGGTGCATATCAGAGCCTAAGCCACCTCTCCACCTTA
ATATTGACAGGAAATCCTATCCAGAATTTAGCCCTGGGAGCCTTTTCTGGACTATCAAGTT
TACAGAAACTGGTAGCTGTGGAGACACATCTGTTATCGCTAGAAAGCTTCCCCATTGGAC
ATCTCAAAACTTTGAAGGACCTTAATGTGGCTCACAATCTAATCCAATCTTTCAAATTACC
TGAGTATTTTTCTAATCTGACCAATCTAGAGCACTTGGACCTTTCTAGTAACAATATTCAA
AATATTTATTGCAAAGACTTGCAGGTTCTACATCAAATGCCCCTACTCAATCTCTCTTTAG
ACCTGTCCCTGAACCCTATAAACTTTATTCAGCCAGGTGCATTTAAAGAAATTAGGCTCCG
TAAGCTGACTTTGAGAAATAATTTTGATAGTTTAAATGTAATGAAAACTTGCATTCACGGT
CTGGCTGGGTTAGAAGTCCATCGTTTGGTTCTGGGAGAATTTAGAAATGAAAGAAATATT
GAAGACTTTGACAAATCTGCTCTGGAGGGCCTGTGCAATTTGACCATCAAAGAATTCCGA
TTAGCATACTTAGACAACTTTCCAGATGATATTATTGACTTATTTAATTGTTTGGTAAATGT
TTCTTCATTTTCCCTGTTGAGTGTGTATATTAAAAGAGTAGAAGACTTTTCTTATAATTTCA
GATGGCAACATTTAGAATTAGTTAACTGTATATTTCAACAGTTTCCTCCACTGAAACTCAA
ATCTCTCAAAAGGCTTACTTTCAGTAAAAACAAAGGTAGGAATCATTTTGCAGAAGTTGA
TCTGCCAAGCCTTGAGTTTCTAGATCTCAGTAGAAATGGCTTGAGTTTCAAAGGTTGCTGT
TCTCAATCTGATTTTGGGACGACCAGCCTAAAGTATTTAGATCTGAGCTTCAATGATGTTA
TTACCATGAGTTCAAACTTCTTAGGCTTAGAACAACTAGAACACTTGGATTTCCAGCATTC
CAATTTGAAACAAATGAGTGAGTTTTCAGTATTTCTATCACTCAGAAACCTCATTTACCTT
GACATTTCTCATACTCACACCAGAGTTGCTTTCAATGGCATCTTTAATGGCTTGTTCAGTCT
CAAAGTCTTGAAAATGGCTGGAAATTCTTTCCAGCAAAACTTCCTTGCAGATATCTTCACA
GATCTGAATAACTTGATATTCCTGGACCTTTCTGAGTGTCAACTGGAGCAGTTGTCTCCAA
CAGCATTTGACTCACTTCCCAGACTTCAGATACTAAATATGAGCCACAACAAGTTCTTTGC
ATTGGATACATTTCCTTATAAGCATCTCTACTCCCTCCACGTTCTGGATTACAGTCTCAATC
ACATAGGGACTTCCAAAAATCAGGAACTACAGCATTTTCCAAGTAGTCTAGCTTTCTTAAA
TCTTACTCAAAATGACTTTGCTTGTACTTGTGAACACCAGAGTTTCCTGCAGTGGATCAAG
GACCAGAGGCGGCTATTGGTGGAAGTTGAACGAATGGAATGCGCAACACCTTTAAATAGG
AAGGGCATACCTGTGCTGAGTTTGAATATCACCTGTCAGATGAGTAAGACCATCATTGGT
GTGTCAGTGCTCAGTGTGCTTGTGGTATCTGTTGTAGCAGTTCTGGTCTATAAGTTCTATTT
TCACCTGATGCTTCTTGCTGGCTGCATAAAGTATGGTAGAGGTGAAAACACCTATGATGCC
TTTGTTATCTACTCAAGCCAGGATGAGGACTGGGTAAGGAATGAACTAGTAAAGAATTTA
GAAGAAGGGGTGCCTCCTTTTCAGCTCTGCCTTCACTACAGAGACTTTATTCCCGGTGTGG
CCATTGCTGCCAACATCATCCATGAAGGTTTCCATAAAAGCCGAAAGGTGATTGTTGTGGT
ATCCCAGCACTTCATCCAGAGCCGCTGGTGTATCTTTGAATATGAGATTGCTCAGACCTGG
CAGTTTCTGAGCAGTCGTGCTGGTATCATCTTCATTGTCCTGCAGAAGGTGGAGAAGTCCC
TGCTCAGGCAGCAGGTGGAGCTGTACCGCCTTCTCAGCAGGAACACCTACCTGGAGTGGG
AGGACAGTGTCCTGGGGAGGCATATCTTCTGGAGGCGACTCAGAAAAGCCCTGCTGAATG
GTAGACCGTGGAGTCCAGAAGGAACAGTGGGTGCAGGATGCGATTAG

FIGURE 8

Squirrel monkey

GTGGTTCCTAACGTTACTTATCAATGCATGGAACTGAATYTCTACAAAATCCCCGACAACA
TCCCCTTCTCAACTAAGAACCTGGACCTGAGCTTTAACCCCCTGAGGCATTTAGGCAGCCA
TAGCTTCTTCAATTTCCCAGAACTGCAGGTGCTGGATTTATCCAGGTGTGACATCCAGACA
ATCGAAGATGGGGCATATCAGAGCCTAAGCCACCTCTCCACCTTAATATTGACAGGAAAT
CCTATCCAGAATTTAGCCCTGGGAGCCTTTTCTGGACTATCAAGTTTACAGAAGCTGGTGG
CTGTGGAGACACATCTGTTATCACTAGAGAACTTCCCCATTGGACATCTCAAAACTTTGAA
GGACCTTAATGTGGCTCACAATCTAATCCAATCTTTCAAATTACCTGAGTATTTTTCTAATC
TGACCAATCTAGAGCACTTGGACCTTTCTAGTAACAATATTCAAAATATTTATTGCAAAGA
CTTGCAGGTTCTACATCAAATGCCCCTACTCAATCTCTCTTTAGACCTGTCCCTGAACCCTA
TAAACTTTATTCAACCAGGTGCGTTTAAAGAAATTAGGCTCCATAAGCTGACTTTGAGAA
ATAATTTTGATAGTTTAAATGCAATGAAAACTTGCATTCAAGGTCTGGCTGGGTTAGAAGT
CCATCGTTTGGTTCTGGGAGAATTTAGAAATGAAAGAAATATTGAAGACTTTGACAAATC
TGCTCTGGAGGGCCTGTGCAATTTGACCATTAATGAATTCCGATTAGCTTACTTAGATGAC
TTTCTAGATGATATTATTGACTTATTTAACTGTTTAGCAAATGTTTCTTCATTTTCCCTGGT
GAATGTGCATATTAAAAGAGTAGAAGACTTTTCTTATAATTTTAGATGGCAACATTTAGAA
TTAGTTAACTGTGTATTTCAACAGTTTCCTCCACTGAAACTCAAATCTCTCAAAAGGCTTA
CTTTCACTGCCAACAAAGGTAGGAATCATTTTTCAGAAGTTGATCTTCCAAGCCTTGAGTT
TCTAGATCTCAGTAGAAATGGCTTGAGTTTCAAAGGTTGCTGTTCTCAATCTGATTTTGGG
ACGACCAGCCTAAAGTATTTAGATCTGAGCTTCAATGACGTTATTACCATGGGTTCAAACT
TCTTAGGCTTAGAACAACTAGAACACTTGGATTTCCAGCATTCCAATTTGAAACAAATGA
GTGAGTTTTCAGTATTCCTATCACTCAGAAACCTCATTTACCTTGACATTTCTCATACTCAC
ACCAGAGTTGCTTTCAATGGCATCTTTAATGGCTTGTTCAGTCTCAAAGTCTTGAAAATGG
CTGGAAATTCTTTCCAGCAAAACTTCCTTGAAGATATCTTCACRGATCTGAATAACTTGAT
ATTCCTGGACCTCTCTGAGTGTCAGCTGGAGCAGTTGTCTCCAACAGCATTTGACTCACTT
CCCAGACTTCGGATACTAAATATGAGCCACAACAACTTCTTTGCATTGGATACATTCCCTT
ACAAGCATCTCTACTCCCTCCAGGTTCTGGATTACAGTCTCAATCATATAGGGACTTCCAA
AAATCAGGAACTGCAGCATTTTCCAAGTAGTCTAGCTTTCTTAAATCTTACTCAAAATGAC
TTTGCTTGTACTTGTGAACACCAGAGTTTCCTGCAGTGGATCAAGGACCAGAGGCGGCTGT
TGGTGGAAGTTGAACAAATGGAATGTGCAACACCTTTAAATAGGAAGGGCATACCTGTGC
TGAGTTTGAATATCACCTGTCAGATGAGTAAGACTATCATTGGTGTGTCAGTGCTCAGTGT
GCTTGTGGTATCTGTTGTAGCAGTTCTGGTCTATAAGTTCTATTTTCACCTGATGCTTCTTG
CTGGCTGCATAAAGTATGGTAGAGGTGAAAACACCTATGATGCCTTTGTTATCTACTCAAG
CCAGGATGAGGACTGGGTAAGGAATGAACTAGTAAAGAATTTAGAAGAAGGGGTGCCTC
CCTTTCAGCTCTGCCTTCACTACAGAGACTTTATTCCCGGTGTGGCCATTGCTGCCAACAT
CATCCATGAAGGTTTCCATAAAAGCCGAAAGGTGATTGTTGTGGTATCTCAGCACTTCATC
CAGAGCCGCTGGTGTATCTTTGAATATGAGATTGCTCAGACCTGGCAGTTTCTGAGCAGTC
GTGCTGGTATCATCTTCATTGTCCTGCAGAAGGTGGAGAAGTCCCTGCTCAGGCAGCAGG
TGGAGCTGTACCGCCTTCTCAGCAGGAACACTTACCTGGAGTGGGAGGACAGTGTCCTGG
GGAGGCACATCTTCTGGAGACGACTCAGAAAAGCCCTGCTGGATGGTAGACCGTGGAATC
CAGAAGGAACAGTGGGTGCAGGATGCGAATAG

FIGURE 9

ABSTRACT

The subject invention comprises a method of identifying an evolutionarily meaningful nucleotide change in a primate's *TLR4* polynucleotide. It further comprises methods for identifying agents that interact with the corresponding evolutionarily meaningful amino acid change so as to modulate the function of the TLR4 polypeptide, thereby attenuating activation of the NF-kB pathway. Such agents are useful in mitigating the LPS mediated response and in the treatment of sepsis, severe sepsis and septic shock.